In view of the above changes and the following remarks, Applicants respectfully request reconsideration of the present rejections.

Claim Objection

The typographic error identified by the Examiner in claim 13 has been corrected, which should obviate the current objection to this claim.

Response to section 112, 2nd paragraph rejection

Claims 13, 16 and 16 are rejected under 35 U.S.C. 112, 2nd paragraph as allegedly being indefinite for reciting the term "metastatic potential." Applicants traverse this rejection.

The test for definiteness under 35 U.S C. 112, 2nd paragraph is whether one skilled in the art, at the time the application is filed, is reasonably apprised of the scope of a claim when that claim is read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 USPQ2d 1081, 1088 (Fed. Cir. 1986).

Here, the claims as amended recite a method for determining the metastatic potential of a cancer in an afflicted patient by measuring the level of activated STAT-3 protein in tumor tissue obtained from the patient. An increased level of STAT-3 protein in the tumor tissue relative to the level of STAT-3 protein in control tissue indicates a higher metastatic potential for the tumor.

Metastasis is a multifactorial process by which tumor cells escape from the primary tumor, disseminate through blood and lymph vessels, evade host immune defenses, and colonize other organs or tissues. Metastatic cells encounter and cross the basement membrane during entry (intravasation) and exit (extravasation) from the blood or lymph vessels. Thus, metastasis is usually described as a three-step model in which metastatic cells must first adhere to a basement membrane, digest the basal lamina with proteolytic enzymes, and then migrate through the vessel wall. See Alberts B, et al., Molecular Biology of the Cell, Garland Publishing, Inc., New York, 1989, pgs. 1200-1201 and Figs. 21-16 and 21-18 (attached).

The facility with which tumor cells can move from the primary tumor to a distant site through the metastatic process is a measure of the "aggressiveness" or "metastatic potential"

of the tumor. Cells of a given tumor may differ in their ability to metastasize. However, the average level of a molecular marker of metastatic potential in a sample of tumor tissue is indicative of the general metastatic potential of the entire tumor. See pgs. 134-137 of Liotta LA et al., "Principles of Molecular Cell Biology of Cancer: Cancer Metastasis," in Cancer: Principles and Practice of Oncology (4th Ed.), DeVita VT et al. (eds.), J.B. Lippincott Co., Philadelphia, 1993 (hereinafter "Liotta"; attached).

The present specification teaches that activated STAT-3 is a molecular marker of a tumor's metastatic potential, and that an increased level of activated STAT-3 in a tumor tissue vs. normal tissue correlates with an increased ability of the tumor to metastasize. See, *e.g.*, on pg. 13, lns. 7-18; pg. 17, lns. 9-10; pg. 18, ln. 26 to pg. 19, ln. 2; and Examples 10 and 11 of the present specification. As recognized in Liotta, *supra*, the average level of a molecular marker in tumor tissue, when that marker has been correlated with the ability of a tumor to metastasize, is a valid measure of the overall metastatic potential of the tumor.

One skilled in the art would therefore understand the metes and bounds of claims 13, 15 and 16 when read in light of specification, and in view of the knowledge in the art regarding metastatic potential discussed above. Claims 13, 15 and 16 are therefore clear and definite, and the 35 U.S.C. 112, 2nd paragraph rejection of these claims should be withdrawn.

Response to the section 103(a) rejection

Claims 13, 15 and 16 are rejected as allegedly rendered obvious by Garcia et al. (1997), *Cell Growth and Differentiation* 8: 1267-1276 ("Garcia") and Takemoto et al. (1997), *PNAS USA* 94: 13897-13902 ("Takemoto"). Applicants respectfully disagree.

The Examiner has rejected the claims under 35 U.S.C. 112, 2nd paragraph as too vague and indefinite to be interpreted by one of ordinary skill in the art. See pg. 3 of the Detailed Action. Under these circumstances, it is improper to also reject the claims as obvious, since a finding of obviousness requires a reliance on speculative assumptions as to the meaning of the claims. Ex parte Simpson, 61 USPQ2d 1009, 1017 (Bd. Pat. App. Int. 2001); Ex parte Brummer, 12, USPQ2d 1653, 1655 (Bd. Pat. App. Int. 1989); In re Steele, 134 USPQ 292 (CCPA 1962).

To the extent that simultaneous rejections under §112, 2nd paragraph and §103(a) are permitted (*i.e.*, the degree of uncertainty is not great and the claims are subject to more than one interpretation), the Examiner is required to set forth the interpretation of the allegedly indefinite phrase that was used in applying the prior art rejection. MPEP §2173.06. No such interpretation was given. Nevertheless, Applicant will address the pending §103(a) rejection below.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in the applicant's disclosure. In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, there is nothing in Garcia or Takemoto that would motivate one of ordinary skill in the art to combine the teachings of these references to produce the presently claimed invention, or which would provide a reasonable expectation of success that the presently claimed methods could be practiced.

Garcia reports increased STAT-3 DNA binding activity in breast cancer cell lines or in rat fibroblast cells which are induced to undergo transformation. Garcia does not correlate the activation of STAT-3 with the ability of the cells to metastasize, but rather characterizes STAT-3 activation as an early event in src-induced oncogenic transformation.

In fact, the entire disclosure of Garcia is directed towards the role of STAT-3 in the transformation of cells by src or other oncoproteins. See, *e.g.*, the following passages from Garcia (citations omitted):

> We and others reported previously that constitutive activation of Stat3 occurs in fibroblasts stably transformed by v-Src, the transforming protein of Rous sarcoma virus. In addition, activation of specific JAKs and STATs has been demonstrated in cells transformed by human T-cell leukemia virus-I and Abl oncoproteins as well as various human blood malignancies, including lymphomas and leukemias. These results raise the possibility that constitutive signaling by certain STAT proteins may participate in the process of cellular transformation. *Pg. 1267, 2nd col.*

> Because STAT activation has been demonstrated to occur in response to both ligand-dependent activation of EGFR and constitutive activation of c-Src, these results further suggest the possibility that STAT signaling may be an important event in malignant progression of human tumors, especially those such as breast carcinomas, which possess frequent activation of these kinases. . . We report that Stat3 activation occurs rapidly after activation of a temperature sensitive v-Src protein, suggesting it is an early event in cellular transformation induced by the oncoprotein. *Pg. 1268, 1st col.*
>
> Fig. 6 shows that elevated Stat3 activity was detected in five of nine breast carcinoma cell lines examined . . . but not in any of three cell lines derived from normal breast epithelial tissue. . . These results are consistent with the profile of activated STATs observed above in fibroblasts transformed by viral oncoproteins, suggesting that similar signaling pathways may participate in activation of STAT proteins during breast cancer progression. *Pg. 1271, 1st col. and paragraph bridging pgs. 1271 and 1272.*
>
> Furthermore, the finding that EGF stimulation can further increase Stat3 activation above the constitutive levels in these breast carcinoma cell lines supports a model in which EGFR and c-Src cooperate in oncogenesis through additive or synergistic activation of Stat3 signaling. *Paragraph bridging pgs. 1273 ands 1274.*
>
> Genetic studies have also directly implicated STAT proteins in tumorigenesis. . . Moreover, we have shown that disrupting Stat3 signaling in NIH 3T3 fibroblasts blocks cell transformation by v-Src, providing evidence that Stat3 is one of the signaling pathways that contributes to Src oncogenesis. Our results reported here further support the notion that activated STAT proteins participate in oncogenic transformation of mammalian cells, including human breast carcinoma cells. *Pg. 1274, last paragraph of 1st col.*

Takemoto discloses that activated STAT-3 is found in some leukemic cells, and that JAK/STAT activation may be associated with leukemic cell proliferation. In particular, the "JAK/STAT activation is associated with replication of leukemic cells and . . . therapeutic approaches aimed at JAK/STAT inhibition may be considered to halt neoplastic growth (Takemoto, abstract)." Takemoto does not correlate STAT-3 activation with metastatic potential, but rather discusses STAT-3 activation only in terms of cellular transformation.

See, *e.g.*, pg. 13901, 2nd col., of Takemoto, which states that "[c]onstitutive activation of JAKs and/or STATs has been correlated with cell transformation in other models of viral transformation."

It was well known at the time the present application was filed that tumorigenesis and metastasis could be under separate genetic control, and that the molecular mechanisms responsible for transformation of normal cells were not necessarily the same as those responsible for metastasis. See, *e.g.*, Liotta, *supra*, pg. 145 (attached), which states that "(oncogenic transfection) models have revealed that some metastasis effector genes can be regulated independently from those that confer tumorigenicity." For example, oncogenes such as h-Ras can induce a metastatic phenotype, but do so through pathways which differ from oncogene-induced tumorigenesis:

> Two observations indicate that he downstream pathways used in *RAS* induction of tumorigenicity and metastasis have dissimilar features. First, the adenovirus *2E1A* gene has been demonstrated to suppress *RAS* induction of metastatic potential with no inhibition of soft agar colony formation or tumorigenicity. Second, cells are capable of being transformed by RAS but do not metastasize. These results are best explained by assuming that invasion and metastasis require activation of a set of effector genes over and above those required for unrestrained growth alone. Liotta, *supra*, pg. 145, 2nd col.

Moreover, evidence that a gene or molecular marker is involved in tumorigenesis does not necessarily mean that the gene or marker is relevant to the metastatic potential of a cell:

> Historically, there have been numerous well-established correlations between the expression of certain tumor markers and advanced disease or poor patient prognosis, suggesting a functional relationship between the marker and tumor progression. In addition, the definition of genomic intervals that exhibit frequent loss or amplification during tumor progression implicates the function of contained genes in tumor progression. While several good candidates have been identified in this way (examples include nm23, KAI1, kiSS-1 [citations omitted]), functional confirmation for a role in metastatic progression has not yet been forthcoming. McClatchey (1999), *Oncogene* 18: 5334-5339 (attached).

Thus, one of ordinary skill in the art would not consider the evidence that STAT-3 activation is correlated with cellular transformation, as presented in Garcia and Takemoto, to mean that STAT-3 activation is also correlated with metastatic potential. The combination of Garcia and Takemoto, therefore, cannot reasonably suggest to one skilled in the art that activated STAT-3 can be used as an indicator of tumor metastatic potential. Moreover, these references do not provide a reasonable expectation that tumor metastatic potential can be successfully predicted from STAT-3 levels. As the Examiner has not established a *prima facie* case of obviousness over Garcia and Takemoto, the 35 U.S.C. section 103(a) rejection of claims 13, 15 and 16 is improper and should be withdrawn.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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BY _____

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Appendix A – "Marked-up" Version of Amended Replacement Paragraph as Required Under 37 C.F.R. 1.121(b)(1)(iii)

Paragraph at pg. 1, lns. 4-5:

This application is a continuation of PCT/US99/06514, filed March 25, 1999 which claims [priority] the benefit of from U.S. provisional application Ser. No. 60/079,755, filed March 27, 1998, now abandoned.

Appendix B – "Marked-up" Version of Amended Claims as Required Under 37 C.F.R. 1.121(c)(1)(ii)

13. (once amended) A method for determining the metastatic potential of a cancer in an afflicted patient [afflicted] comprising:

1) obtaining a sample of tumor tissue from the patient;

2) obtaining a sample of normal tissue from the patient;

3) determining the level of activated STAT-3 protein in [a] the sample of tumor tissue and in the sample of normal tissue from the patient,

wherein an increased level of [said] activated STAT-3 protein in the tumor tissue as compared to the control tissue [being indicative of the] indicates an increased metastatic potential of said tumor.